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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/591,791	GALA ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *9-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/6/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-8 in the reply filed on June 11, 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

In the reply of June 11, 2009, Applicant further elected the species of Spy0160 and Ecs0036, as well as SEQ ID NO: 14 and 230. With respect to claims 5 and 7, Applicant's election of only the species of SEQ ID NO: 14 and 230 was confirmed in a telephone interview with Che Chereskin on July 28, 2009.

2. Claims 1-19 are pending.

Claims 9-19 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 1-8 have been examined herein. In particular, claim 4 has been examined only to the extent that it reads on the marker Spy0160, claim 5 has been examined to the extent that the marker is SEQ ID NO: 14, claim 6 has been examined to the extent that the marker is Ecs0036, and claim 7 has been examined to the extent that the marker is SEQ ID NO: 230. The remaining markers recited in claims 4-7 are withdrawn from consideration as being directed to a non-elected invention, there being no allowable generic or linking claim.

Claim Rejections - 35 USC § 112 second paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 6 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 4 is indefinite over the recitation of "Spy0160." This phrase is not clearly defined in the specification and there is no art recognized definition for this phrase. The specification provides examples of what may be encompassed by Spy0160, but does not appear to provide a limiting definition. For example, in Table 1, the specification lists Spy0160, and then recites PurA, Marker I, SEQ ID NO: 1-62 and 326-359 and SEQ ID NO: 63. It is unclear from these teachings whether Spy0160 is limited to any PurA gene or any sequence comprising a PurA gene, to any one of or to all of SEQ ID NO: 1-62 and 326-359 or SEQ ID NO: 63. Since SEQ ID NO: 63 is a sequence found in gram-negative organisms, this recitation further confounds the meaning of Spy0160 since the specification indicates that the Spy0160 marker is conserved in Gram-positive bacteria. The specification (page 9) also teaches that a molecular marker may have 50% or more sequence identity to "an original sequence." Accordingly, it is unclear as to whether Spy0160 constitutes an original sequence or if it encompasses any sequence having 50% identity to SEQ ID NO: 1-63 and/or 326-359, or to any PurA gene or any other unspecified Spy0160 sequence. The specification (page 12) discusses probes that consist of 15-50 nucleotides and thereby it is unclear as to whether the marker Spy0160 consists of a full length marker or gene or the full length sequence of one or more of SEQ ID NO: 1-63 and 326-329, or to any 15mer fragment thereof. At page 21, the

specification states: "The **Spy0160** sequence (marker I) from Streptococcus pyogenes (accession number: AE006485.1; position 3201 to 4030) is part of an open reading frame homologous for the gene purA." Given this teaching it is unclear as to whether the Spy0160 marker is considered to include or be limited to the fragment of nucleotides 3201-4030 of "accession number: AE006485.1." In this instance, it would also be unclear as to what constitutes such a marker because the specification defines the marker in terms of a sequence present in an unspecified database. To the extent that the claims seek to refer to the information provided in NCBI GenBank databases entries, these entries include a variety of information, including one or more different flanking sequences, start and stop positions for coding sequences, source of organism, strain, serotype, etc. However, it is unclear as to which characteristics disclosed for each entry are intended to be encompassed by the recited accession number. Further, the information in databases varies over time and is not fixed. Therefore the recitation of the accession numbers, such as GenBank accession numbers, in the absence of a clear definition in the specification, renders the claims unclear and indefinite.

B. Claim 6 is indefinite over the recitation of "Ecs0036." This phrase is not clearly defined in the specification and there is no art recognized definition for this phrase. The specification provides examples of what may be encompassed by Ecs0036, but does not appear to provide a limiting definition. For example, in Table 1, the specification lists Ecs0036, and then recites carB, Marker V, the sequences found in Gram-negative bacteria of SEQ ID NO: 194-232, 238-239, 242-254, and 431-442 and then recites the overlapping gram positive bacteria sequences of SEQ ID NO: 233-237, 240-241 and

255. It is unclear from these teachings whether Ecs0036 is limited to any carB gene or any sequence comprising a carB gene, to any one of or to all of SEQ ID NO: 194-232, 238-239, 242-254, and 431-442 or SEQ ID NO: 233-237, 240-241 and 255. Since SEQ ID NO: 233-237, 240-241 and 255 are sequences found in gram-positive organisms, this recitation further confounds the meaning of Ecs0036 since the specification indicates that the Ecs0036 marker is conserved in Gram-negative bacteria and is a marker for Gram-negative bacteria. The specification (page 9) also teaches that a molecular marker may have 50% or more sequence identity to "an original sequence." Accordingly, it is unclear as to whether Ecs0036 constitutes an original sequence or if it encompasses any sequence having 50% identity to SEQ ID NO: 194-232, 238-239, 242-254, and 431-442 , or 233-237, 240-241 and 255, or to any carB gene or any other unspecified Ecs0036 sequence. The specification (page 12) discusses probes that consist of 15-50 nucleotides and thereby it is unclear as to whether the marker Ecs0036 consists of a full length marker or gene or the full length sequence of one or more of SEQ ID NO: 194-232, 238-239, 242-254, and 431-442 , or SEQ ID NO: 233-237, 240-241 and 255, or to any 15mer fragment thereof. At page 24, the specification states: "Another sequence is the **Ecs0036** sequence (marker V) from Escherichia coil O157:H7 (accession no. AP002550; from position 35200 to 36200). It is believed that this sequence encodes the large carbamoyl-synthetase unit, an enzyme which catalysis the synthesis of carbamoyl phosphate, from glutamine, bicarbonate and two ATP molecules through a mechanism which requires several successive steps." Given this teaching it is unclear as to whether the Ecs0036 marker is considered to include or be limited to the

fragment of nucleotides 35200 to 36200 of accession number AP002550. In this instance, it would also be unclear as to what constitutes such a marker because the specification defines the marker in terms of a sequence present in an unspecified database. To the extent that the claims seek to refer to the information provided in NCBI GenBank databases entries, these entries include a variety of information, including one or more different flanking sequences, start and stop positions for coding sequences, source of organism, strain, serotype, etc. However, it is unclear as to which characteristics disclosed for each entry are intended to be encompassed by the recited accession number. Further, the information in databases varies over time and is not fixed. Therefore the recitation of the accession numbers, such as GenBank accession numbers, in the absence of a clear definition in the specification, renders the claims unclear and indefinite.

C. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the steps required to accomplish the objective of diagnosing a bacterial infection. That is, the claim recites a single step of screening for the presence of two conserved molecular markers, but does not recite a step of diagnosing a bacterial infection, as is required by the preamble of the claim.

Claim Rejections - 35 USC § 112 first paragraph – Written Description

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6 and 8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

In analyzing the claims for compliance with the written description requirements of 35 U.S.C. 112, first paragraph, a determination is made as to whether the specification contains a written description sufficient to show they had possession of the full scope of their claimed invention at the time the application was filed.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof.

In the present situation, claims 1-3 and 8 are drawn to methods for detecting any microorganism in a sample comprising detecting the presence or absence of at least two conserved sequences. Claims 2 and 8 are limited to methods wherein the microorganism is a bacteria. Claim 3 is limited to methods wherein one marker is conserved in gram-positive bacteria and a second marker is conserved in gram-negative bacteria. Claims 1-3 and 8 do not define the conserved marker in terms of any particular structural features, such as their nucleotide sequence or their length. The claims very generally describe the markers in terms of being conserved, but the claims

do not indicate the gene from which the markers are obtained, the microorganism(s) which the markers detect, the degree of conservation of the markers (e.g., conserved among all members of a genus, conserved among only species within a genus, conserved among only strains within a species, conserved among all prokaryotic organisms, etc). The specification (page 9) states that the markers are preferably for the detection of bacteria, but may detect any microorganism (e.g., fungi or DNA viruses or RNA viruses). Accordingly, the claims encompass an extremely large genus of markers that have not been defined in terms of their specific structural or functional properties.

Claim 4 is limited to methods wherein the marker is a marker conserved in gram-positive bacteria and is the "Spy0160" marker. As discussed above, the specification does not clearly define this marker and thereby it is has been given its broadest reasonable interpretation. The Spy0160 marker is considered to encompass any fragment of 15 or more nucleotides of a PurA gene from any organism, or any sequence selected from SEQ ID NO: 1-62, 326-359 and 63, and any sequence comprising such sequences, and sequences having 50% identity thereto. Claim 6 is limited to methods wherein the marker is a marker for gram-negative bacteria and is a "Ecs0036" marker. Again, in the absence of a clear definition for this marker in the specification, the Ecds0036 marker has been given its broadest reasonable interpretation. The Ecs0036 marker is thereby considered to encompass any fragment of 15 or more nucleotides of a carB gene from any organism, or any sequence selected from SEQ ID NO: 194-232, 238-239, 242-254, and 431-442 , or SEQ ID NO: 233-237, 240-241 and 255, and any sequence comprising such sequences, and sequences having 50% identity thereto

Accordingly, claims 4 and 6 also encompass a significantly large genus of markers that have not been clearly defined in terms of any relevant identifying characteristics, such as their particular nucleotide sequence, length, hybridization specificity, etc..

The genus of markers is considered to be significantly large given the vast number of possible microorganisms, including yeasts, viruses, gram-positive and gram-negative bacteria, that the conserved molecular markers are to detect. The size of the genus is further expanded by the fact that the claims encompass markers that share only 50% identity "with the original sequence" (page 9) and markers that comprise/include only 15 nucleotides of an original sequence (page 12) and thereby may be flanked by nucleotides of any identity and length.

Regarding gram-positive conserved markers, the specification describes 4 regions obtained from bacteria which include regions that are present in gram-positive bacteria – Spy0160, Spy1372, SpyM3_0902/SpyM3_0903, and Spy1527. As discussed above, the regions are described by an acronym but are not clearly defined in the specification. The specification (Table 1) exemplifies sequences from these regions that are found in gram-positive bacteria: for Spy0160 – SEQ ID NO:1-62, 326-359; for Spy1372 – SEQ ID NO: 64-107, 109-111, 117-129, 137, 145-148, 360-395, 397-399; for SpyM3_0902/SpyM3_0903 – SEQ ID NO: 150-180 and 404-412; for Spy1527 – SEQ ID NO: 181-193 and 413-425. However, the specification teaches that these sequences are not actually specifically conserved in gram-positive microorganisms because the sequences are also present in gram-negative microorganisms. Specifically, the

specification teaches that the Spy0160 region is present as SEQ ID NO: 63 in gram-negative bacteria and Spy1372 is present as SEQ ID NOs: 108, 112-116, 130-136, 138-144, 396, and 400-403 in gram-negative bacteria. The Spy1372 region is found in the non-bacterial genome of Cryptococcus neoformans (SEQ ID NO: 149; see Table 1). The specification exemplifies a method of detecting "molecular marker I (purA) in Gram-positive bacteria" (Figure 1). However, the specification does not clearly indicate the identity of the probe used to detect the gram-positive bacteria. Further, the specification does not teach use of such a probe to analyze gram-negative bacteria, to thereby establish that the probe detects only gram-positive and not gram-negative bacteria. The specification does not identify particular fragments of the recited SEQ ID NOs in Table 1 which are conserved in gram-positive bacteria. Nor does the specification identify any particular regions of conservation, such that sequences having only 50% identity thereto would still meet the criteria of being conserved in gram-positive bacteria. In Example 3 (page 25), the specification identifies degenerate primers consisting of SEQ ID NO: 462 and 463 and the use of these primers to amplify PurA sequences of gram-positive bacteria. The specification does not clearly indicate whether these primers amplify gram-negative bacteria.

Regarding gram-negative conserved markers, the specification describes 4 regions obtained from bacteria which include regions that are present in gram-negative bacteria – Ecs0036, H15576, EG10839/EG11396, and H10019. As discussed above, the regions are described by an acronym but are not clearly defined in the specification. The specification (Table 1) exemplifies sequences from these regions that are found in

gram-negative bacteria: for Ecs0036 – SEQ ID NO: 194-232, 238-239, 242-254, and 431-442; for H15576 – SEQ ID NO: 256-277, 426-430; for EG10839/EG11396- SEQ ID NO: 278-303 and 443-451; and for H10019 – SEQ ID NO: 304-325 and 452-461. However, the specification teaches that these sequences are not actually specifically conserved in gram-negative microorganisms because the sequences are also present in gram-negative microorganisms. Specifically, the specification teaches that the elected Ecs0036 region is present as SEQ ID NO: 233-237, 240-241 and 255 in gram-positive bacteria. The specification exemplifies a method of detecting "molecular marker V (carB) in Gram-negative bacteria" (Figure 8). However, the specification does not clearly indicate the identity of the probe used to detect the gram-positive bacteria. Further, the specification does not teach use of such a probe to analyze gram-negative bacteria, to thereby establish that the probe detects only gram-negative positive and not gram-positive bacteria. The specification does not identify particular fragments of the recited SEQ ID NOs in Table 1 which are conserved in gram-negative bacteria. Nor does the specification identify any particular regions of conservation, such that sequences having only 50% identity thereto would still meet the criteria of being conserved in gram-negative bacteria. In Example 4 (page 25-26), the specification does identify degenerate primers consisting of SEQ ID NO: 472 and 473 and the use of these primers to amplify CarB sequences in gram-negative bacteria. The specification does not indicate whether these primers also amplify gram-positive bacteria.

The specification (page 28, Table 4) further describes probes for detecting and distinguishing between Bacillus species B. cereus, B. thuringiensis, and B. anthracis.

The exemplified probes do not detect all gram-positive bacteria and thereby are not conserved amongst gram-positive bacteria. The specification (page 29) also describes the primers of SEQ ID NO: 23 and 478 which amplify S. aureus sequences and the probe of SEQ ID NO: 479 which distinguishes between the strains of S. aureus of MRSA MW2 and MRSA COL versus Mu-50 and N315. However, the specification does not teach that the sequences of SEQ ID NO: 23, 478 and 479 are present in other gram-positive bacteria and thereby are conserved in gram-positive bacteria. Rather, these sequences appear to be specific for only one type of gram-positive bacteria – i.e., S. aureus.

Accordingly, the specification has described by its complete structure sequences present in gram-positive bacteria and gram-negative bacteria. For the Spy0016 region, the specification describes the sequences of SEQ ID NO:1-62, 326-359 by their complete structure. For the Ecs0036 region, the specification describes the sequences of SEQ ID NO: 194-232, 238-239, 242-254 by their complete structure. However, these full length sequences appear to be present only in a single species from which they were isolated. The specification does not teach that the full length molecules are present and conserved in a representative number of gram-positive bacteria or gram-negative bacteria. Thereby, the exemplified full length sequences are not considered to be conserved among species of gram-positive bacteria or gram-negative bacteria and thus do not constitute conserved markers. Note that the specification (e.g., page 4, lines 6-9) indicates that the conserved markers are to be used to identify bacteria "in a Gram-specific way."

The specification does describe by its complete structure the particular degenerate primers of SEQ ID NO: 462 and 463 for the PurA gene which amplify gram-positive species, but are not necessarily specific for gram-positive species, and SEQ ID NO: 472 and 473 for the CarB gene which amplify gram-negative species. Although, the specification has not established that such markers can be used to identify bacteria "in a Gram-specific way."

No additional members of the claimed genus have been sufficiently described in terms of any other relevant identifying characteristics.

While the prior art does exemplify particular primers and probes that are present in members of a particular genus of bacteria or are present in all bacteria, the specification itself does not disclose such sequences and thereby cannot be relied upon as providing support for these sequences. For instance, the prior art of Klaschik et al (Journal of Clinical Microbiology. November 2002. 40: 4304-4307; cited in the IDS) discloses a first probe (ISN2) that is specific for gram-negative microorganisms and a second probe (ISP2)) that is specific for gram-positive microorganisms. However, the present specification does not contemplate methods which use the ISN2 and ISP2 probes of Klaschik. Accordingly, the specification cannot be relied upon for providing support for methods for detecting a microorganism by detecting the ISN2 and ISP2 sequences of Klaschik.

Further, the specification does not describe any conserved markers from fungi or from viruses by their complete structure or by any other relevant identifying characteristics. The specification does not describe any markers that specifically detect

only gram-positive bacteria or only gram-negative bacteria by their complete structure or by any other relevant identifying characteristics.

It is noted that the specification also teaches the general methodology for obtaining probes which consist of fragments of a know sequence or which share sequence identity, such as 50% identity, with a know sequence. However, possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features. See University of Rochester, 358 F.3d at 927, 69 USPQ2d at 1895.

This finding is also emphasized in *Ex Parte Kubin* (No. 2007-0819, Bd. Pat. App. & Int. May 31, 2007), wherein it is stated that :

"Although there is often significant overlap" between the enablement and written description requirements, "they are nonetheless independent of each other." University of Rochester, 358 F.3d at 921, 69 USPQ2d at 1891. An "invention may be enabled even though it has not been described." Id. Such is the situation here. While we conclude one skilled in the art would have been able to make and use the full scope of claim 73 through routine experimentation, we find Appellants did not describe the invention of claim 73 sufficiently to show they had possession of the claimed genus of nucleic acids. See, e.g., Noelle v. Lederman, 355 F.3d 1343, 1348, 69 USPQ2d 1508, 1513 (Fed. Cir. 2004) ("invention is, for purposes of the 'written description' inquiry, whatever is now claimed").

Thereby, a showing of how to potentially identify and make other markers is not sufficient to establish that Applicant's were in possession of the invention as broadly claimed.

Moreover, the naming of a marker in terms of its functional attributes is not sufficient to describe that marker. More than a statement of biological function is required to satisfy the 35 USC 112 first paragraph, written description requirement for a genus of DNA molecules. See e.g. Amgen Inc. v. Chuzai Pharmaceutical Co. Ltd., 18 U.S.P.Q.2d 1016, 1027 (CAFC 1991); and Fiers v. Revel, 25 U.S.P.Q.2d 1601, 1604-05 (CAFC 1993). In Amgen v. Chuzai, the Court of Appeals for the Federal Circuit stated that "it is not sufficient to define (a DNA) solely by its principal biological property, e.g. encoding of human erythropoietin." Id. at 1021. Rather, what is necessary is that (the applicant) provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims." Id. at 1027. In these statements, the court has expressly stated that a DNA molecule must be described by means of description other than by naming the encoded protein to satisfy the 35 USC 112 first paragraph written description requirement. More recently, the Federal Circuit again took this position. In the case University of California v. Eli Lilly and Co., 43 U.S.P.Q.2d 1398, at 1406 (1997), the court stated that defining a CDNA by its function 'tis only a definition of a useful result rather than a definition of what achieves that result." The court also stated that such a description does not define any structural features commonly possessed by members of the genus that distinguish them from others."

Additionally, the specification does not disclose a clear structure-function relationship between the claimed markers and the function of being conserved in gram-positive or gram-negative bacteria. Knowledge that a particular sequence is present in a bacteria does not allow one to envision which particular fragments of that molecule or which sequences sharing only 50% identity with that molecule will be present in other members of the gram-positive or gram-bacteria genus, and thereby will constitute conserved sequences. No common structure has been disclosed regarding what constitutes a conserved sequence other than the degenerate primers of SEQ ID NO: 462 and 463 for the PurA gene and SEQ ID NO: 472 and 473 for the CarB gene.

Again, the claimed genus is significantly large including markers of any length and identity for any virus, fungi or bacteria, or for any gram-positive or gram-negative microorganism. In the absence of any real structure-function relationship and in the absence of a representative number of species of the claimed genus of conserved markers, there is insufficient descriptive support for the currently claimed genus of any conserved marker for any microorganism or any conserved marker for gram–positive microorganisms and any conserved marker for gram-negative microorganisms.

The decisional law in this area has been very consistent. The Federal Circuit in Lilly, Fiers, Rochester and many other cases has determined that the written description issue applies to situations where the definition of the subject matter of the claims fails to provide description commensurate with the genus. Recent case law directly supports this rejection. As the District Court in University of Rochester v. G.D. Searle & Co., Inc. (2003 WL 759719 W.D.N.Y.,2003. March 5, 2003.) noted "In effect, then, the '850

patent claims a method that cannot be practiced until one discovers a compound that was not in the possession of, or known to, the inventors themselves. Putting the claimed method into practice awaited someone actually discovering a necessary component of the invention." This is similar to the current situation since the breadth of the current claims comprises any conserved marker for any microorganism which the present inventors were not in the possession of, or which were not known to the inventors.

As noted in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), the Federal Circuit concluded that:

"...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

With respect to the present invention, there is no record or description which would demonstrate conception of conserved markers other than the particular degenerate primers of SEQ ID NO: 462 and 463 for the PurA gene which amplify gram-positive species, but are not necessarily specific for gram-positive species, and SEQ ID NO: 472 and 473 for the CarB gene which amplify gram-negative species, but which are not necessarily specific for gram-negative species. Therefore, the claims fail to meet the written description requirement because the claims encompass a significantly large genus of mRNAs and proteins which are not described in the specification.

Claim Rejections - 35 USC § 112 - Enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (i) methods for detecting *Bacillus anthracis* Sterne comprising obtaining a nucleic acid sample, analyzing the nucleic acid sample for the presence or absence of nucleic acids comprising SEQ ID NO: 14 and detecting the presence of nucleic acids comprising SEQ ID NO: 14 as indicative of the presence of Bacillus anthracis Sterne; and (ii) methods for detecting *Francisella tularensis* comprising obtaining a nucleic acid sample, analyzing the nucleic acid sample for the presence or absence of nucleic acids comprising SEQ ID NO: 230 and detecting the presence of nucleic acids comprising SEQ ID NO: 230 as indicative of the presence of *Francisella tularensis*,

does not reasonably provide enablement for methods for detecting any microorganism using any conserved marker, any conserved gram-positive or any conserved gram-negative marker, any conserved Spy0160 or any conserved Ecs0036 marker, or methods which detect any microorganism by detecting the markers of SEQ ID NO: 14 or SEQ ID NO: 230. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the

predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claims 1-3 and 8 are drawn to methods for detecting any microorganism in a sample comprising detecting the presence or absence of at least two conserved sequences. Claims 2 and 8 are limited to methods wherein the microorganism is a bacteria. Claim 3 is limited to methods wherein one marker is conserved in gram-positive bacteria and a second marker is conserved in gram-negative bacteria. Claims 1-3 and 8 do not define the conserved marker in terms of any particular structural features, such as their nucleotide sequence or their length. The claims very generally describe the markers in terms of being conserved, but the claims do not indicate the gene from which the markers are obtained, the microorganism(s) which the markers detect, the degree of conservation of the markers (e.g., conserved among all members of a genus, conserved among only species within a genus, conserved among only strains within a species, conserved among all prokaryotic organisms, etc). The specification (page 9) states that the markers are preferably for the detection of bacteria, but may detect any microorganism (e.g., fungi or DNA viruses or RNA viruses). Accordingly, the claims encompass an extremely large genus of markers that have not been defined in terms of their specific structural or functional properties.

Claim 4 is limited to methods wherein the marker is a marker conserved in gram-positive bacteria and is the "Spy0160" marker. As discussed above, the specification

does not clearly define this marker and thereby it is has been given its broadest reasonable interpretation. The Spy0160 marker is considered to encompass any fragment of 15 or more nucleotides of a PurA gene from any organism, or any sequence selected from SEQ ID NO: 1-62, 326-359 and 63, and any sequence comprising such sequences, and sequences having 50% identity thereto. Claim 6 is limited to methods wherein the marker is a marker for gram-negative bacteria and is a "Ecs0036" marker. Again, in the absence of a clear definition for this marker in the specification, the Ecds0036 marker has been given its broadest reasonable interpretation. The Ecs0036 marker is thereby considered to encompass any fragment of 15 or more nucleotides of a carB gene from any organism, or any sequence selected from SEQ ID NO: 194-232, 238-239, 242-254, and 431-442 , or SEQ ID NO: 233-237, 240-241 and 255, and any sequence comprising such sequences, and sequences having 50% identity thereto

Accordingly, claims 4 and 6 also encompass a significantly large genus of markers that have not been clearly defined in terms of any relevant identifying characteristics, such as their particular nucleotide sequence, length, hybridization specificity, etc..

The genus of markers is considered to be significantly large given the vast number of possible microorganisms, including yeasts, viruses, gram-positive and gram-negative bacteria, that the conserved molecular markers are to detect. The size of the genus is further expanded by the fact that the claims encompass markers that share only 50% identity "with the original sequence" (page 9) and markers that

comprise/include only 15 nucleotides of an original sequence (page 12) and thereby may be flanked by nucleotides of any identity and length.

Claims 5 and 7 are directed to methods for detecting any microorganism (i.e., any bacteria, fungus or virus) by detecting the markers SEQ ID NO: 14 and SEQ ID NO: 230, respectively.

Nature of the Invention:

The claims are drawn to methods for detecting microorganisms by assaying for the presence of conserved markers. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F. 3d 1316, 1330 (Fed Cir. 2001).

Teachings in the Specification and State of the Art:

It is first noted that the specification (e.g., page 4, lines 6-9) indicates that the conserved markers are to be used to identify bacteria "in a Gram-specific way."

Regarding the elected invention of SEQ ID NO: 14, the sequence listing indicates that this sequence was isolated from *Bacillus anthracis* Sterne. Regarding SEQ ID NO: 230, the Sequence Listing indicates that this sequence was isolated from *Francisella tularensis*.

Regarding gram-positive conserved markers, the specification describes 4 regions obtained from bacteria which include regions that are present in gram-positive bacteria – Spy0160, Spy1372, SpyM3_0902/SpyM3_0903, and Spy1527. As discussed above, the regions are described by an acronym but are not clearly defined in the specification. The specification (Table 1) exemplifies sequences from these regions that

are found in gram-positive bacteria: for Spy0160 – SEQ ID NO:1-62, 326-359; for Spy1372 – SEQ ID NO: 64-107, 109-111, 117-129, 137, 145-148, 360-395, 397-399; for SpyM3_0902/SpyM3_0903 – SEQ ID NO: 150-180 and 404-412; for Spy1527 – SEQ ID NO: 181-193 and 413-425. However, the specification teaches that these sequences are not actually specifically conserved in gram-positive microorganisms because the sequences are also present in gram-negative microorganisms. Specifically, the specification teaches that the Spy0160 region is present as SEQ ID NO: 63 in gram-negative bacteria and Spy1372 is present as SEQ ID NOs: 108, 112-116, 130-136, 138-144, 396, and 400-403 in gram-negative bacteria. The Spy1372 region is found in the non-bacterial genome of Cryptococcus neoformans (SEQ ID NO: 149; see Table 1). The specification exemplifies a method of detecting "molecular marker I (purA) in Gram-positive bacteria" (Figure 1). However, the specification does not clearly indicate the identity of the probe used to detect the gram-positive bacteria. Further, the specification does not teach use of such a probe to analyze gram-negative bacteria, to thereby establish that the probe detects only gram-positive and not gram-negative bacteria. The specification does not identify particular fragments of the recited SEQ ID NOs in Table 1 which are conserved in gram-positive bacteria. Nor does the specification identify any particular regions of conservation, such that sequences having only 50% identity thereto would still meet the criteria of being conserved in gram-positive bacteria. In Example 3 (page 25), the specification identifies degenerate primers consisting of SEQ ID NO: 462 and 463 and the use of these primers to amplify PurA sequences of gram-positive

bacteria. The specification does not clearly indicate whether these primers amplify gram-negative bacteria.

Regarding gram-negative conserved markers, the specification describes 4 regions obtained from bacteria which include regions that are present in gram-negative bacteria – Ecs0036, H15576, EG10839/EG11396, and H10019. As discussed above, the regions are described by an acronym but are not clearly defined in the specification. The specification (Table 1) exemplifies sequences from these regions that are found in gram-negative bacteria: for Ecs0036 – SEQ ID NO: 194-232, 238-239, 242-254, and 431-442; for H15576 – SEQ ID NO: 256-277, 426-430; for EG10839/EG11396- SEQ ID NO: 278-303 and 443-451; and for H10019 – SEQ ID NO: 304-325 and 452-461. However, the specification teaches that these sequences are not actually specifically conserved in gram-negative microorganisms because the sequences are also present in gram-negative microorganisms. Specifically, the specification teaches that the elected Ecs0036 region is present as SEQ ID NO: 233-237, 240-241 and 255 in gram-positive bacteria. The specification exemplifies a method of detecting "molecular marker V (carB) in Gram-negative bacteria" (Figure 8). However, the specification does not clearly indicate the identity of the probe used to detect the gram-positive bacteria. Further, the specification does not teach use of such a probe to analyze gram-negative bacteria, to thereby establish that the probe detects only gram-negative positive and not gram-positive bacteria. The specification does not identify particular fragments of the recited SEQ ID NOs in Table 1 which are conserved in gram-negative bacteria. Nor does the specification identify any particular regions of conservation, such that sequences having

only 50% identity thereto would still meet the criteria of being conserved in gram-negative bacteria. In Example 4 (page 25-26), the specification does identify degenerate primers consisting of SEQ ID NO: 472 and 473 and the use of these primers to amplify CarB sequences in gram-negative bacteria. The specification does not indicate whether these primers also amplify gram-positive bacteria.

The specification (page 28, Table 4) further describes probes for detecting and distinguishing between Bacillus species B. cereus, B. thuringiensis, and B. anthracis. The exemplified probes do not detect all gram-positive bacteria and thereby are not conserved amongst gram-positive bacteria. The specification (page 29) also describes the primers of SEQ ID NO: 23 and 478 which amplify S. aureus sequences and the probe of SEQ ID NO: 479 which distinguishes between the strains of S. aureus of MRSA MW2 and MRSA COL versus Mu-50 and N315. However, the specification does not teach that the sequences of SEQ ID NO: 23, 478 and 479 are present in other gram-positive bacteria and thereby are conserved in gram-positive bacteria. Rather, these sequences appear to be specific for only one type of gram-positive bacteria – i.e., S. aureus.

While the prior art does exemplify particular primers and probes that are present in members of a particular genus of bacteria or are present in all bacteria, the specification itself does not disclose such sequences and thereby cannot be relied upon as providing support or enablement for these sequences. For instance, the prior art of Klaschik et al discloses a first probe (ISN2) that is specific for gram-negative microorganisms and a second probe (ISP2)) that is specific for gram-positive

microorganisms. However, the present specification does not contemplate methods which use the ISN2 and ISP2 probes of Klaschik. Accordingly, the specification cannot be relied upon for providing support or enablement for methods for detecting a microorganism by detecting the ISN2 and ISP2 sequences of Klaschik.

The Predictability or Unpredictability of the Art :

The art of making and using probes that are conserved among all microorganisms, including viruses, fungi and bacteria and probes that are present in all gram-positive or gram-negative organisms is highly unpredictable. Knowledge that a particular sequence is present in one particular species does not allow one to immediately envision specific variants having 50% identity thereto or nucleic acids comprising 15mer fragments thereof that will be conserved in all other microorganisms, or in all other bacteria or in all other gram-positive or gram-negative bacteria.

The teachings in the specification support the unpredictability of identifying sequences that are conserved among all members of a group. For example, the specification (Table 1) teaches that the gram-positive Spy0160 marker is also present in the gram-negative microorganism of *Escherichia coli* (i.e., SEQ ID NO: 63). Similarly, the specification teaches that the gram-negative marker of Ecs0036 is also present in the gram-positive microorganisms having the sequence of SEQ ID NO: 233-237, 24-241 and 255 – i.e., for example, the gram-positive microorganisms Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium avium, Corneybacterium efficiens, Corneybacterium glutamicum, and Corneybacterium diphtheriae.

Amount of Direction or Guidance Provided by the Specification and Degree of Experimentation:

The specification teaches the well known methodologies for aligning nucleic acid sequences and identifying sequences present in one organism but absent in other organisms. However, such teachings are generic in nature, and there are no specific teachings of how to predictably make and use nucleic acids particular sequences as conserved markers wherein the sequences may share only 50% identity with an "original sequence" and wherein the sequences may include only 15 nucleotides of an original sequence, flanked by nucleotides of any length and having any identity. The specification does not identify any particular sequences other than the degenerate primers of SEQ ID NO: 462 and 463 and 472 and 473 which are conserved in gram-positive and gram-negative bacteria. Even with respect to these degenerate primers, the specification has not established that the primers amplify and detect only gram-positive or gram-negative bacteria, since the specification provides no information regarding the cross-hybridization properties of these primers.

While the specification teaches that SEQ ID NO: 14 was isolated from *Bacillus anthracis* Sterne and that SEQ ID NO: 230 was isolated from *Francisella tularensis*, the specification does not teach that these same sequences are present in other gram-positive or gram-negative bacteria and thereby can be detected as specifically indicative of any microorganism, or any gram-positive bacteria (with respect to SEQ ID NO: 14, or any gram-negative bacteria (with respect to SEQ ID NO: 230).

Further, while the specification exemplifies specific PurA gene sequences from various species of gram-positive bacteria (SEQ ID NO: 1-62 and 326-359), and exemplifies specific CarB gene sequences from various gram-negative bacteria (SEQ ID NO: 194-232, 238-239, 242-254 and 431-442), the specification does not provide any guidance as to particular sequences within these genes that are conserved among gram-positive or gram-negative bacteria, respectively, and which could thereby be used to detect bacteria in a "gram-specific" manner. Thus, there is no guidance provided in the specification as to which 15 mer fragments of these sequences are conserved only between gram-positive or gram-negative bacteria and which thereby distinguish gram-positive from gram-negative bacteria and vice versa. There is also no guidance provided in the specification as to which sequences having only 50% identity with the gram-positive bacterial sequences of SEQ ID NO: 1-62 and 326-359, or the gram-negative bacterial sequences of SEQ ID NO: 194-232, 238-239, 242-254 and 431-442, and which thereby distinguish gram-positive from gram-negative bacteria and vice versa.

While one could generate a significantly large genus of nucleic acids in which nucleotides of any identity are added to the 5' or 3' terminus of 15 mer fragments of SEQ ID NO: 1-62 and 326-359, 194-232, 238-239, 242-254 and 431-442, or in which up to 50% of the nucleotides therein are substituted, and then assay each of these nucleic acids to try to determine if any of the nucleic acids are conserved among all microorganisms, or all bacteria, or all gram-positive or gram-negative bacteria, such trial-by-error experimentation is considered to be undue. Providing methods for

searching for additional nucleic acids and trying to determine which nucleic acids are conserved and useful for detecting microorganisms in a "gram-specific" manner is not equivalent to teaching how to make and use specific nucleic acids.

Working Examples:

The specification exemplifies the particular sequence of SEQ ID NO: 14 and teaches that this sequence was isolated from *Bacillus anthracis* Sterne. The specification also exemplifies the particular sequence of SEQ ID NO: 230 and teaches that the sequence was isolated from *Francisella tularensis*. However, the specification does not provide any working examples in which the presence of SEQ ID NO: 14 is indicative of the presence of any other gram-positive bacteria or any other microorganism or in which the presence of SEQ ID NO: 230 is detected as indicative of the presence of any other gram-negative bacteria or any other microorganism.

The specification exemplifies specific PurA gene sequences from various species of gram-positive bacteria (SEQ ID NO: 1-62 and 326-359), and exemplifies specific CarB gene sequences from various gram-negative bacteria (SEQ ID NO: 194-232, 238-239, 242-254 and 431-442. However, the specification does not provide any examples in which these sequences are used to detect only gram-positive or gram-negative microorganisms - i.e., to detect bacteria in a gram-specific manner.

The specification also exemplifies the use of the degenerate primers of SEQ ID NO: 462 and 463 to amplify PurA sequences of gram-positive bacteria. However, the specification does not provide any working examples in which the primers are used to detect only gram-positive bacteria. The specification exemplifies the use of the

degenerate primers of SEQ ID 472 and 473 to amplify CarB sequences of gram-negative bacteria. However, the specification does not provide any working examples in which the primers are used to detect only gram-negative bacteria.

Conclusions:

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the specification does not teach one of skill in the art how to use the disclosed nucleic acids for the purpose set forth in the specification (e.g., at page 4) of detecting a bacteria in a gram-specific manner. Further, the claims do not bear a reasonable correlation to the scope of enablement because the specification teaches PurA and CarB gene sequences present in particular gram-positive or gram-negative bacteria, including the elected sequences of SEQ ID NO: 14 and 230, whereas the claims encompass a significantly large genus of conserved markers to detect all microorganisms, or all bacteria, or all members of the

group of gram-positive bacteria or all members of the group of gram-negative bacteria. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art, it would require undue experimentation for one of skill in the art to make and use the broadly claimed invention.

Further, to the extent that the claims seek to define the conserved molecular markers Spy0160 and Ecs0036 in terms of the sequences set forth in a database, this sequence information would be critical or essential to the practice of the invention, but would not be enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

In particular, at page 21, the specification states: "The **Spy0160** sequence (marker I) from Streptococcus pyogenes (accession number: AE006485.1; position 3201 to 4030) is part of an open reading frame homologous for the gene purA." At page 24, the specification states: "Another sequence is the **Ecs0036** sequence (marker V) from Escherichia coil O157:H7 (accession no. AP002550; from position 35200 to 36200)."

Thereby, to the extent that the recitation in the claims of Spy0160 and Ecs0036 intends to refer to the sequences set forth in the recited accession numbers at pages 21 and 24 of the specification, the recitation of the accession numbers constitutes an attempt to incorporate by reference subject matter which is contained within a database accession number, such as a NCBI record. This recitation constitutes an improper incorporation by reference of essential material since it is material that is necessary to describe the claimed invention. However, essential material may not be incorporated by

reference to non-patent publications, such as the NCBI database (MPEP 608.01)(p). Specifically, MPEP 608.01(p)[R-2] states that "While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention." Therefore, the claims are rejected for failure to comply with the enablement requirement because the specification fails to provide essential subject matter for the practice of the claimed invention – i.e., the Spy0160 sequence set forth in accession number: AE006485.1; position 3201 to 4030, and the Ecs0036 sequence set forth in accession no. AP002550; positions 35200-36200.

6. The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper – i.e., the incorporation of the accession numbers AE006485.1, positions 3201-4030 (page 21) and accession number AP002550, positions 35200-36200 (page 24) by reference to an unspecified database. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Klaschik et al (Journal of Clinical Microbiology. November 2002. 40: 4304-4307; cited in the IDS).

Klaschik et al discloses a method for detecting and identifying a microorganism in a sample comprising contacting the sample, such as water, urine, plasma and sputum with a first probe (ISN2) that is specific for gram negative microorganisms and with a second probe (ISP2)) that is specific for gram positive microorganisms (i.e., probes that detect conserved molecular markers), detecting complexes formed between target nucleic acids in the sample and the probes as indicative of the presence of gram-positive or gram-negative microorganisms (see abstract and page 4304, col. 2). Klaschik teaches that ISN2 hybridizes to a consensus (i.e., conserved) sequence present in the 16S rRNA of gram negative bacteria and that ISP2 hybridizes to a consensus (i.e., conserved) sequence present in the 16S rRNA of gram positive bacteria (page 4304 and Figures 1 and 2). Accordingly, Klaschik et al anticipate the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/

Primary Examiner, Art Unit 1634